hPTH(1-34) therapy improves healing in MRSA-infected fractures in Type 2 Diabetes Mellitus mice: An experimental study for therapeutic proof of concept

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INTRODUCTION: Type 2 Diabetes mellitus (T2DM) impairs fracture healing and is associated with higher rates of delayed union and non-union and susceptibility to infection, which is devastating to the fracture healing response. While parathyroid hormone (PTH) effectively improves fracture healing in T2DM animal models, it has never been studied in the context of infected fracture non-union. In the present investigation, the potential of teriparatide in improving infected fracture healing is demonstrated in both diabetic and non-diabetic mouse models of tibial shaft fracture.

METHODS:

T2DM mice were induced by chronic, high-fat-high-sugar (HFHS) diet for 6 months. Glucose intolerance was verified. Both HFHS and lean-fed control mice underwent transverse open osteotomy of the tibia. MRSA (1×10^6 CFU) infected with tibia open fracture surgery. Mice were treated with vancomycin (30 mg/kg) and rifampin (20 mg/kg) combination for 3 days. After antibiotics treatment, daily subcutaneous injection of PTH (40 ug/kg) was additionally given for 4 weeks before fractured tibiae were harvest at 4 weeks. Tibia tissues were measured in callus formation and union changes using plain AP & Lateral x-rays for RUST scores (**Figure 1**). μCT analysis was done for measuring bone volume (BV), total volume (TV), BV/TV, connectivity density (conn-dens), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular separation (Tb. Sp), temporomandibular disorders (TMD), and bone surface/bone volume (BS/BV) parameters (**Figure 2**). Additional histologic examination was done for 2-week specimens. Differences between diabetic and wild-type groups for blood glucose testing, glucose tolerance testing, body weight, and uninterrupted fracture healing parameters were calculated with unpaired T-test. $P < 0.05$ was considered statistically significant.

RESULTS:

Higher rates of radiographic fracture mal-union and non-union were observed in diabetic mice compared to their lean non-diabetic counterparts, with concomitant reductions in micro-computed tomography (μCT) parameters of bony architecture and biomechanical strength. An MRSA-inoculated surgical tibia fracture model was used to simulate open fracture, after which mice were treated with a combination of antibiotics (vancomycin and rifampin) and adjunctive teriparatide treatment.

DISCUSSION AND CONCLUSION:

Adjuvant teriparatide treatment following conventional systemic antibiotic therapy improved fracture healing, the rate of bony union, and numerous parameters of bone microarchitecture in T2DM tibial fractures that were infected with MRSA. Our results provide mechanistic insights into DM in the context of osteomyelitis and suggest that teriparatide may constitute a viable therapeutic agent to improve bony union and bone microarchitecture to prevent the development of septic non-union under diabetic conditions.